REMARKS/ARGUMENTS

Claims 1, 3-19 and 21-27 are pending. Claims 1 and 10 are amended. Claim 27 is new. Support for the amendment to claim 1 can be found at least in the claim as originally filed. Support for the amendments to claim 10 and new claim 27 can at least be found in claim 10 as originally filed. Support for the amendment to the specification can be found at least in claim 1 as originally filed.

No new matter has been added.

Remarks regarding the Election/Restriction

The Examiner has withdrawn claims 25 and 26 from consideration because Applicant allegedly constructively elected the originally presented invention. The Examiner cites 37 CFR 1.142(b) and MPEP 821.03 for reference. Applicant respectfully disagrees with the Examiner's restriction and with the citations used to justify said restriction. Because the instant application is a US national stage of a PCT application, the cited rules do not apply. The correct rules for the instant application is PCT Rule 13 wherein "unity of invention" is the determining standard for election/restriction requirements. Claims 25 and 26 share a least the combination of a), b), c) and d), and the ratio of polyvinyl acetate to polyvinylpyrrolidone as a corresponding "special technical feature" and as such, the restriction is in error. Applicant respectfully requests withdrawal of the restriction and rejoinder of claims 25 and 26.

Remarks regarding 35 USC §112 ¶2

Claims 1, 3-19 and 21-24 stand rejected for allegedly being indefinite. Applicant respectfully disagrees.

The Examiner asserts that "[i]t is unclear what is meant by "facilitating delayed release."" Applicant directs the Examiner to Webster's Unabridged Dictionary of the English Language, page 690 for a definition of the term "facilitate" (attached hereto) - the ordinary meaning of the term. In this regard, Applicant respectfully asserts that the phrase "facilitates said delayed release" would be well understood by one of ordinary skill in the art based on the disclosure of

the specification and the art available at the time of filing, for example Webster's dictionary. Accordingly, Applicant respectfully requests withdrawal of this rejection.

The Examiner also rejects claim 1 under §112 ¶2 because it allegedly lacks antecedent basis. Applicants asserts that the lack of antecedent basis alone does not render a claim indefinite under §112 ¶2 and this rejection is error and should be withdrawn (*Energizer Holdings v. ITC*, 435 F.3d 1366 (Fed. Cir. 2006)). Nonetheless, while neither agreeing with the Examiner's reasoning for nor the validity of this §112 ¶2, Applicant amended claim 1 to facilitate prosecution of the instant U.S. patent application. Accordingly, the rejection is moot and should be withdrawn.

Claim 1 has also been amended to delete the phrase "low or high molecular weight."

The Examiner also alleges that "it is not clear what constitutes a "formulated mixture" as opposed to a mixture that is not "formulated."" Applicant respectfully asserts that the phrase "formulated mixture" would be well known to one of ordinary skill in the art. Moreover, in the Office Action of 22 December 2005, the Examiner refers to the "instant formulation" (page 3) and the "formulation of Kolter" (page 3) when suggesting amendments. Additionally, on page 4, in the context of dismissing Applicant's argument that Ortega does not teach, suggest or disclose a formulated mixture, such as in the instant claimed invention, the Examiner responds with the following:

> However, 4,837,034 is clearly directed to tablets which contain a mixture of many ingredients, which a person of ordinary skill in the art would consider to be a formulated mixture

Applicant respectfully asserts that it is apparent from the Examiner's comments alone that one of ordinary skill in the art would understand what a formulated mixture and thus, the rejection is moot.

Further, Applicant provides guidance and cites references in the specification. For instance, on page 3, lines 17-21, Applicant describes the instant formulated mixture. Applicant also references US 5,490,990 wherein said cited art reference discloses in its examples formulated mixtures.

Accordingly, because the formulated mixture of the instant claimed invention would be well known to the skilled artisan, the rejection is in error and should be withdrawn.

Claim 10 has been amended and the rejection for this claim is moot.

Remarks regarding 35 USC §102

Claims 1, 3-19 and 21-24 stand rejected for allegedly being anticipated by Kolter et al. Applicant respectfully disagrees.

Anticipation can only be established by a single prior art reference which discloses each and every element of the claimed invention (*See*, *RCA Corp. v. Applied Digital Data Systems, Inc.,* 730 F.2d 1440, 1444 (Fed. Cir. 1984)). "The identical invention must be shown in as complete detail as is contained in the patent claim" (*Richardson v. Suzuki Motor Co.,* 868 F.2d 1226, 1236 (Fed. Cir. 1989)). It is not enough, however, that the reference discloses all the claimed elements in isolation. Rather, as stated by the Federal Circuit, the cited art reference must disclose each element of the claimed invention "arranged as in the claim" (*Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)).

The Examiner alleges that the composition of Kolter et al. discloses the same amounts as that recited in the instant claims and therefore such claims are not novel. However, Applicant respectfully asserts that the of the instant claims under 35 USC §102(b) is not proper. The requirements for anticipation with regard to ranges is discussed in MPEP §2131.03. In the case at hand, there are no examples disclosed in Kolter which are within the instant claimed ranges. The Examiner appears to rely heavily on the indication in Kolter that binder content is from 0.5 to 20%. Therefore, the Examiner would allege there is overlap at the 20% range point with respect to the instant claims. In this regard, Kolter et al. also teaches, as indicated in column 2, lines 18-20, that "the binder content in the presentation is to be **less than 20%** by weight" (emphasis added).

Such a slight overlap, if any at all, in one criterion of the claims is, given the totality of the circumstances, not sufficient for a proper anticipation rejection in this case. This is because the instant claimed range is from 20%-80%, and therefore there is only at most, a slight overlap at one point of the range. However, the instant claims also require "water soluble polymers or

lipophilic additives." Kolter merely indicates 0-20% by weight of another water soluble or water swellable substance. Thus, no water soluble or water swellable substance need be added according to Kolter et al. Therefore, one of ordinary skill in the art would have to modify or choose amongst the ranges indicated by Kolter et al. in order to attempt to arrive at the claimed invention, and so one of skill in the art cannot immediately envisage the claimed invention. Consequently, Kolter et al. fails to teach to disclose each and every element of the instant claimed invention **as arranged in the claims.**

Additionally, as Applicant asserted in the Office Action reply of 21 October 2005, The mixture of Kolter et al. is formulated in such a way that the resulting dosage forms show rapid or immediate release of the active ingredient. This rapid release is caused by the overall composition of the formulation which preferably only contains up to 15 % of the formulated mixture of polyvinyl acetate and polyvinyl pyrrolidone in combination with other additives. According to examples 3, 4, and 5 of Kolter et al., from 98.8 to 99.5 % of the active ingredients are released after 30 minutes. Accordingly, Kolter et al. fails to teach delayed release formulated mixture of the instant claimed invention and thus fails to anticipate the claims.

For at least the reasons asserted above, Kolter et al. fails to teach, suggest or disclose each any every element of the instant claimed invention, as arranged in the claim. Consequently, Kolter et al fails to anticipate the instant claimed invention. Accordingly, Applicant respectfully requests withdrawal of the 102 (b) rejection.

Remarks regarding 35 USC §103

Claims 1, 3-19 and 21-24 stand rejected for allegedly being obvious in view of Kolter et al. in light of Ortega. Applicant respectfully disagrees.

To establish *prima facie* obviousness, the Examiner must show in the prior art some suggestion or motivation to make the claimed invention, a reasonable expectation for success in doing so, and a teaching or suggestion of each Claim element (*See, e.g., In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ 2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Royka,*

490 F.2d 981, 180 USPQ 580 (CCPA 1974)). However, mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole (*In re Rouffet*, 149 F.3d 1350, 1355, 1357 (Fed. Cir. 1998)). Rather, to establish a *prima facie* case of obviousness based on a combination of elements disclosed in the prior art, the Examiner must articulate the basis on which it concludes that it would have been obvious to make the claimed invention (*Id.*). In practice, this requires that the Examiner "explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious" (*Id.* at 1357-59). This entails consideration of both the "scope and content of the prior art" and "level of ordinary skill in the pertinent art" aspects of the *Graham* test.

Known compositions do not render an invention obvious simply because they could be combined; to establish a *prima facie* case of obviousness, the Examiner must provide a rationale for said combination. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination (*In re Mills*, 916 F.2d 680 (Fed. Cir. 1990)). Applicant respectfully asserts that there is no motivation to combine the cited art references the Examiner has used as a basis for the § 103 rejections.

Kolter et al. is directed to instant release or quick release preparations. These preparations are completely opposite to the delayed release preparation of the instant claimed invention. Therefore, one of ordinary skill in the art would not modify Kolter et al. to create a delayed release preparation, because it is directed to immediate release preparations. Even if adding a binder caused delayed release properties, one of ordinary skill in the art would have no motivation to do so, because Kolter et al. is directed to instant release preparation.

However, the Examiner has taken the position that 1 hour, as in claim 1 of Kolter et al., suggests delayed release (Office Action 03 July 2006, page 5). Applicant respectfully asserts that the 0.1 to 1 hours claimed in Kolter does not suggest delayed release. The Examiner is directed to the reply filed 21 October 2005, and the document "General Information in Vitro and In Vivo Evaluation of Dosage Forms," page 1925, column 1, 4th full paragraph. In short the

reference states that quick release tests generally last from 30-60 minutes. Further, for testing modified release dosage, the same document indicates an early time point would be 1 to 2 hours to show that dose dumping is not probable. Because 1 to 2 hours is considered "early," a 1 hour maximum would be reasonable to suggest immediate release. Applicant respectfully asserts that because Kolter et al. is directed to immediate release preparations, one of ordinary skill in the art would fail to be motivated to make the combinations suggested by the Examiner to practice the instant claimed invention.

Indeed, the combination of art references proposed by the Examiner changes the principle of operation of the instant claimed invention. If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious (*In re Ratti*, 270 F.2d 810 (CCPA 1959)).

The combination proposed by the Examiner would change the delayed release formulation of the instant claimed invention to one of immediate release. Consequently, the combination suggested by the Examiner would change the principle of operation of the instant claimed invention. Accordingly, a *prima facie* case has not been established and the rejection is moot. Withdrawal of the 103 rejection is hereby requested.

Furthermore, regarding Ortega and Remington, the Examiner has alleges that it is obvious that by adding binder, one of ordinary skill in the art could optimize release rate. Moreover, the Examiner asserts that Remington "teaches that although a variety of material can be used as binders, the purpose of binders is nonetheless the same." Applicant respectfully directs the Examiner to Remington, 20th edition, pages 860-861(attached hereto) which states, in part, the following:

> Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators. They impart a cohesiveness to the tablet formulation that ensures the tablet remaining intact after compression, as well as improving the free-flowing qualities by the formulation of granules of desired hardness and size.

Applicant respectfully asserts that while the Examiner's statement that "the purpose of

binders is nonetheless the same," may be accurate, said purpose is "to impart cohesive qualities." Simply modifying the amount of a randomly chosen binder does not impart delayed release properties. Accordingly, the combination of Ortega and Kolter et al. is improper and the 103 rejection should be withdrawn.

Conclusion

Applicants respectfully submit that the present application is in condition for allowance, which action is courteously requested. Please charge any shortage in fees due in connection with the filing of this paper to Deposit Account 14.1437. Please credit any excess fees to such account.

Respectfully submitted,
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WEBSTER'S UNABRIDGED DICTIONARY *of the* ENGLISH LANGUAGE

The dictionary entries are based on the Second Edition of
The Random House Dictionary of the English Language

RHR
PRESS

outer or upper side of a fabric; right side. **16.** the acting, striking, or working surface of an implement, tool, etc. **17.** *Geom.* any of the bounding surfaces of a solid figure: *a cube has six faces.* **18.** Also called **working face.** *Mining.* the front or end of a drift or excavation, where the material is being or was last mined. **19.** *Print.* **a.** the working surface of a type, of a plate, etc. See diag. under **type. b.** Also called **typeface.** any design of type, including a full range of characters, as letters, numbers, and marks of punctuation, in all sizes: *Caslon is one of the most popular faces.* See table under **typeface. c.** Also called **typeface.** the general style or appearance of type: *broad or narrow face.* **20.** *Naut., Aeron.* the rear or after side of a propeller blade (opposed to *back*). **21.** *Fort.* either of the two onter sides that form the salient angle of a bastion or the like. See diag. under **bastion. 22.** *Crystall.* any of the plane surfaces of a crystal. **23.** *Electronics.* faceplate (def. 3). **24.** *Archaic.* sight; presence: *to flee from the face of the enemy.* **25. face to face, a.** facing or opposite one another: *We sat face to face at the table.* **b.** in an open, personal meeting or confrontation: *The leaders spoke face to face about a reduction in nuclear arms.* **26. face to face with,** in close proximity to; narrowly escaping; confronting: *face to face with death.* **27. fly in the face of.** See **fly**[1] (def. 21). **28. get out of someone's face** (usually used imperatively) **a.** *Southern U.S.* go away!; leave. **b.** *Slang.* to stop bothering or annoying someone. **29. in the face of, a.** in spite of; notwithstanding: *She persevered in the face of many obstacles.* **b.** when confronted with: *They were steadfast in the face of disaster.* **30. lose face,** to suffer disgrace, humiliation, or embarrassment: *It was impossible to apologize publicly without losing face.* **31. make a face,** to grimace, as in distaste or contempt; contort one's face in order to convey a feeling or to amuse another: *She made a face when she was told the work wasn't finished. The children made me laugh by making faces.* **32. on the face of it,** to outward appearances; superficially; seemingly: *On the face of it, there was no hope for a comeback.* **33. put on a bold face,** to give the appearance of confidence or assurance: *Everyone knew that he had been fired, even though he put on a bold face.* Also, **put a bold face on. 34. save face,** to avoid disgrace, humiliation, or embarrassment: *She tried to save face by saying that the bill had never arrived.* **35. set one's face against,** to disapprove strongly of; oppose: *My parents have set their face against my becoming an actress.* **36. show one's face,** to make an appearance; be seen: *I would be ashamed to show my face in such an outlandish outfit. Just show your face at the party and then you can leave.* **37. to one's face,** in one's presence; brazenly; directly: *Tell him to his face that he's a liar!*

—*v.t.* **38.** to look toward or in the direction of: *to face the light.* **39.** to have the front toward or permit a view of: *The building faces Fifth Avenue. The bedroom faces the park.* **40.** to confront directly: *to be faced with a problem; to face the future confidently.* **41.** to confront courageously, boldly, or impudently (usually fol. by *down* or *out*): *He could always face down his detractors.* **42.** to oppose or to meet defiantly: *to face fearful odds; Army faces Navy in today's football game.* **43.** to cover or partly cover with a different material in front: *They faced the old wooden house with brick.* **44.** to finish the edge of a garment with facing. **45.** to turn tbe face of (a playing card) upwards. **46.** to dress or smooth the surface of (a stone or the like). **47.** to cause (soldiers) to turn to the right, left, or in the opposite direction. **48.** *Ice Hockey.* (of a referee) to put (the puck) in play by dropping it between two opposing players each having his or her stick on the ice and facing the goal of tbe opponent.

—*v.i.* **49.** to turn or be turned (often fol. by *to* or *toward*): *She faced toward the sea.* **50.** to be placed with the front in a certain direction (often fol. by *on, to,* or *toward*): *The house faces on the street. The barn faces south.* **51.** to turn to the right, left, or in the opposite direction: *Left face!* **52.** *Ice Hockey.* to face the puck (often fol. by *off*). **53. face down,** to confront boldly or intimidate (an opponent, critic, etc.). **54. face off,** *Ice Hockey.* to start a game or period with a face-off. **55. face the music.** See **music** (def. 9). **56. face up to, a.** to acknowledge; admit: *to face up to the facts.* **b.** to meet courageously; confront: *He refused to face up to his problems.* [1250–1300; (n.) ME < AF, OF < VL **facia,* for L *faciēs* FACIES; (*v.*) late ME *facen,* deriv. of the n.] **—face′a·ble,** *adj.*

—Syn. 1. FACE, COUNTENANCE, VISAGE refer to the front of the (usually human) head. The FACE is the combination of the features: *a face with broad cheekbones.* COUNTENANCE, a more formal word, denotes the face as it is affected by or reveals the state of mind, and hence often signifies the look or expression on the face: *a thoughtful countenance.* VISAGE, still more formal, refers to the face as seen in a certain aspect, esp. as revealing seriousness or severity: *a stern visage.* **2.** appearance, aspect, mien. **7.** exterior. **14.** façade. **43.** veneer.

face′ an′gle, *Geom.* the angle formed by two successive edges of a polyhedron. [1910–15]

face′ bow′ (bō), *Dentistry.* a device for determining the relationship of the maxillae to the mandibular joint. Also, **face′bow′.** [1935–40]

face′ card′, the king, queen, or jack of playing cards. [1665–75]

face-cen·tered (fās′sen′tərd), *adj. Crystall.* (of a crystal structure) having lattice points on the faces of the unit cells. Cf. **body-centered.** [1910–15]

face·cloth (fās′klôth′, -kloth′), *n., pl.* **-cloths** (-klôthz′, -klothz′, -klôths′, -kloths′). washcloth. Also called, *Brit.,* **face′ flan′nel.** [1595–1605; FACE + CLOTH]

faced (fāst), *adj.* having a specified kind of face or number of faces (uaually used in combination): *a sweet-faced child; the two-faced god.* [1490–1500; FACE + -ED[3]]

face·down (*adv.* fās′doun′; *n.* fās′doun′), *adv.* **1.** with the face or the front or upper surface downward: *He was lying facedown on the floor. Deal the cards facedown on the table.* —*n.* **2.** Also, **face′-down′.** *Informal.* a direct confrontation; showdown. [1930–35; (def. 1) FACE + DOWN[1]; (def. 2) n. use of v. phrase *face down*]

face′ gear′, *Mach.* a disklike gear having teeth cut on the face more or less radially and engaging with a spur or helical pinion, the axis of which is at right angles to it.

face-hard·en (fās′här′dn), *v.t.* to harden tbe surface of (metal), as by chilling or casehardening. [1895–1900]

face·less (fās′lis), *adj.* **1.** without a face: *a faceless apparition.* **2.** lacking personal distinction or identity: *a faceless mob.* **3.** unidentified or unidentifiable; concealing one's identity: *a faceless kidnapper.* [1560–70; FACE + -LESS] **—face′less·ness,** *n.*

face-lift (fās′lift′), *n.* **1.** Also, **face′ lift′ing. face′-lift′ing.** plastic surgery on the face for elevating sagging tissues and eliminating wrinkles and other signs of age; rhytidectomy. **2.** a renovation or restyling, as of a room or building, intended to give an attractive, more up-to-date appearance. —*v.t.* **3.** to perform a face-lift upon. **4.** to renovate or restyle in order to give a fresher, more modern appearance: *Our old offices have been face-lifted with new furniture.* Also, **face′lift′.** [1920–25, *Amer.*]

face′ mask′, **1.** *Sports.* the protective equipment, usually made of steel or plastic, that guards the face, as the steel cage worn by a baseball catcher or the molded plastic covering worn by a hockey goalkeeper. **2.** any of various similar devices to shield the face, sometimes attached to or forming part of a helmet, as that worn by workers engaged in a hazardous activity. Also, **face′·mask′.** [1905–10; FACE + MASK]

face-nail (fās′nāl′), *v.t.* to secure with nails driven perpendicular to the surface. Cf. **toenail** (def. 4).

face-off (fās′ôf′, -of′), *n. Ice Hockey.* **1.** tbe act of facing the puck, as at the start of a game. **2.** an open confrontation. [1895–1900; n. use of v. phrase *face off*]

face·plate (fās′plāt′), *n.* **1.** (on a lathe) a perforated plate, mounted on the live spindle, to which the work is attached. **2.** the part of a protective headpiece, as a diver's or astronaut's helmet, that covers the upper portion of the face, often of transparent material and sometimes movable. **3.** Also called **face.** *Electronics.* the glass front of a cathode ray tube upon which the image is displayed. **4.** a protective plate, as one surrounding an electric outlet or light switch. Cf. **switch plate.** [1835–45; FACE + PLATE[1]]

face′ pow′der, a cosmetic powder used to give a met finish to the face. [1855–60]

fac·er (fā′sər), *n.* **1.** a person or thing that faces. **2.** *Informal.* a blow in the face. **3.** *Brit. Informal.* an unexpected major difficulty, dilemma, or defeat. [1505–15; FACE + -ER[1]]

face-sav·er (fās′sā′vər), *n.* something that saves one's prestige or dignity: *Allow him the face-saver of resigning instead of being fired.* [1940–45] **—face′-sav′·ing,** *n., adj.*

fac·et (fas′it), *n., v.,* **-et·ed, -et·ing** or (*esp. Brit.*) **-et·ted, -et·ting.** —*n.* **1.** one of the small, polished plane surfaces of a cut gem. **2.** a similar surface cut on a fragment of rock by the action of water, windblown sand, etc. **3.** aspect; phase: *They carefully examined every facet of the argument.* **4.** *Archit.* any of the faces of a column cut in a polygonal form. **5.** *Zool.* one of the corneal lenses of a compound arthropod eye. **6.** *Anat.* a small, smooth, flat area on a hard surface, esp. on a bone. **7.** *Dentistry.* a small, highly burnished area, usually on the enamel surface of a tooth, produced by abrasion between opposing teeth in chewing. —*v.t.* **8.** to cut facets on. [1615–25; < F *facette* little face. See FACE, -ET]

fa·cete (fə sēt′), *adj. Archaic.* facetious. [1595–1605; < L *facētus* clever, witty] **—fa·cete′ly,** *adv.* **—fa·cete′ness,** *n.*

fa·ce·ti·ae (fə sē′shē ē′), *n.pl.* amusing or witty remarks or writings. [1520–30; < L, pl. of *facētia* something witty. See FACETE, -IA]

face′ time′, **1.** a brief appearance on television. **2.** a brief face-to-face meeting, esp. with someone important. [1975–80]

fa·ce·tious (fə sē′shəs), *adj.* **1.** not meant to be taken seriously or literally: *a facetious remark.* **2.** amusing; humorous. **3.** lacking serious intent; concerned with something nonessential, amusing, or frivolous: *a facetious person.* [1585–95; FACETE + -IOUS; see FACETIAE] **—fa·ce′tious·ly,** *adv.* **—fa·ce′tious·ness,** *n.*

—Syn. 2. See **humorous.**

fac′et joint′, *Anat.* any of the four projections that link one vertebra of the spine to an adjacent vertebra.

face-to-face (fās′tə fās′), *adj.* **1.** with the fronts or faces toward each other. **2.** involving close contact or direct opposition: *a face-to-face confrontation.* [1300–50; ME]

face′ tow′el, a small towel for the face. [1920–25]

face·up (fās′up′), *adv.* with the face or the front or upper surface upward: *Place the cards faceup on the table.* [1960–65; FACE + UP]

face val·ue (fās′ val′yo͞o *for 1;* fās′ val′yo͞o *for 2*), **1.** the value printed on the face of a stock, bond, or other financial instrument or document. **2.** apparent value: *Do not accept promises at face value.* [1875–80]

fa·cia (fā′shə), *n. Chiefly Brit.* dashboard (def. 1). Also, **fascia.** Also called **fa′cia board′.** [1880–85; sp. var. of FASCIA, perh. through confusion with L *faciēs,* E FACE, FACIAL, etc.]

fa·cial (fā′shəl), *adj.* **1.** of the face: *facial expression.* **2.** for the face: *a facial cream.* —*n.* **3.** a treatment to beautify the face. [1600–10; 1910–15 for def. 3; < ML *faciālis.* See FACE, -AL[1]] **—fa′cial·ly,** *adv.*

fa′cial an′gle, *Craniom.* the angle formed from nasion to prosthion at its intersection plane of the Frankfurt horizontal. [1815–25]

fac′ial in′dex, *Craniom.* the ratio of the bre face to its height. [1885–90]

fa′cial nerve′, *Anat.* eitber one of the sev of cranial nerves composed of motor fibers tha muscles of the face except those used in chewin 20]

fa′cial neural′gia, *Pathol.* See **tic doulour**

fa′cial tis′sue, a soft, disposable peper tissu cleansing the face or for use as a handkerchie 30]

fa·ci·es (fā′shē ēz′, -shēz), *n., pl.* **fa·ci·es. 1.** appearance, as of an animal or vegetable group. the appearance and characteristics of a sedimen posit, esp. as they reflect the conditions and envi of deposition and serve to distinguish the depo contiguous deposits. Cf. **metamorphic facies.** a facial expression characteristic of a disease o logical condition. **4.** *Archaeol.* a distinctive ph prehistoric cultural tradition. [1350–1400, for a sense; ME < L: form, figure, appearance, face, *facere* to make]

fac·ile (fas′il or, *esp. Brit.,* -il), *adj.* **1.** moving, working, proceeding, etc., with ease, sometimes perficiality: *facile fingers; a facile mind.* **2.** easi performed, used, etc.: *a facile victory; a facile* **3.** easy or unconstrained, as manners or perso fable, agreeable, or complaisant; easily influenced *ile temperament; facile people.* [1475–85; < L that can be done, easy, equiv. to *fac(ere)* to do, -*ilis* -ILE] **—fac′ile·ly,** *adv.* **—fac′ile·ness,** *n.*

—Syn. 1. smooth, flowing, fluent; glib. **2.** sup **3.** bland, suave; urbane.

fa·ci·le prin·ceps (fä′ki le′ pring′keps; *Eng.* lē prin′seps), *Latin.* easily the first or best.

fa·ci·lis de·scen·sus A·ver·no (fä′ki lis de so͞os ä wer′nō; *Eng.* fas′ə lis di sen′sas a vû *Latin.* (the) descent to hell is easy; it is easy to ta downward path. Vergil, *Aeneid,* 6:126.

fa·cil·i·tate (fə sil′i tāt′), *v.t.,* **-tat·ed, -tat·ing.** make easier or less difficult; help forward (an ac process, etc.): *Careful planning facilitates any k work.* **2.** to assist tbe progress of (a person). [16 FACILIT(Y) + -ATE[1]] **—fa·cil′i·ta′tive,** *adj.*

fa·cil·i·ta·tion (fə sil′i tā′shen), *n.* **1.** the act or ess of facilitating. **2.** *Physiol.* the lowering of resi in a neural pathway to an impulse, resulting from p ous or simultaneous stimulation. [1610–20; FACIL + -ION]

fa·cil·i·ta·tor (fə sil′i tā′tər), *n.* **1.** a person or that facilitates. **2.** a person responsible for leadi coordinating the work of a group, as one who le group discussion: *Each committee will meet wi facilitator.* [1815–25; FACILITATE + -OR[2]]

fa·cil·i·ty (fe sil′i tē), *n., pl.* **-ties. 1.** Often, **faci a.** something designed, built, installed, etc., to ser specific function affording a convenience or ser *transportation facilities; educational facilities; a re search facility.* **b.** something that permits the easier formance of an action, course of conduct, etc.: *to pro someone with every facility for accomplishing a task lack facilities for handling bulk mail.* **2.** readiness ease due to skill, aptitude, or practice; dexterity: *to co pose with great facility.* **3.** ready compliance: *Her fa ity in organizing and directing made her an excellent pervisor.* **4.** an easy-flowing manner: *facility of style* the quality of being easily or conveniently done or formed. **6.** Often, **facilities.** *Informal.* a rest room one for use by the public, as in a theater or restau **7.** freedom from difficulty, controversy, misunders ing, etc.: *facility of understanding.* [1375–1425; late *facilite* (< MF) < L *facilitās.* See FACILE, -ITY]

fac·ing (fā′sing), *n.* **1.** a covering in front, for or ment, protection, etc., as an outer layer of stone brick wall. **2.** a lining applied to the edge of a gar for ornament or strengthening. **3.** material turned ward or inward, as a cuff or hem. **4. facings,** cover of e different color applied on the collar, cuffs, or parts of a military coat. [1350–1400; ME; see -ING[1]]

fac′ing tool′, *Metalworking.* a lathe tool for ing a plane surface et right angles to the axis of [1880–85]

fa·çon (fᴀ sôɴ′), *n., pl.* **-çons** (-sôɴ′). *French.* fashion; manner; style. **2.** workmanship; make 1805]

fa·con·ne (fas′ə nā′, fas′ə nā′), *adj.* **1.** (of a having a small and elaborate pattern. —*n.* **2.** having a faconne pattern or motif. **3.** the small elaborate pattern on a faconne fabric. [1890–95; *çonné,* ptp. of *façonner* to work, FASHION; see -ED]

F.A.C.P., Fellow of the American College of Physicia Also, **FACP**

FACS, 1. *Biol.* fluorescence-activated cell sorter chine that sorts cells according to whether or not have been tagged with antibodies carrying a fluoresc dye, separating tbe cells mechanically in a vibrating zle, imparting a positive or negative charge to cells fluoresce, and then passing the cells through an ele field to deflect them into eppropriate containers Also, **F.A.C.S.** Fellow of the American College of Sur geons.

facsim., facsimile.

fac·sim·i·le (fak sim′ə lē), *n., v.,* **-led, -le·ing.** —*n.* **1.** an exact copy, as of e book, painting, or manu script. **2.** Also called **fax.** *Telecommunications.* method or device for transmitting documents, drawings photographs, or the like, by means of radio or telephone for exact reproduction elsewhere. **b.** an image transmit ted by auch a method. **3.** dropout (def. 5). —*v.t.* reproduce in facsimile; make a facsimile of. Also, **fax.** *Telecommunications.* **a.** (of an image by means of facsimile: *focsimile moil.* **b.** (of a method

CONCISE ETYMOLOGY KEY: <, descended or borrowed from; >, whence; b., blend of, blended; c., cognate with; cf., compare; deriv., derivative; equiv., equivalent; imit., imitative; obl., oblique; r., replacing; s., stem; sp., spelling, spelled; resp., respelling, respelled; trans., translation; ?, origin unknown; *, unattested; ‡, probably earlier than. See the full key inside the front cover.

20 TH EDITION

Remington: The Science and Practice of Pharmacy

ALFONSO R GENNARO
Chairman of the Editorial Board
and Editor

lets must have a number of additional attributes such as appearance, hardness, disintegration ability, appropriate dissolution characteristics, and uniformity, which also are influenced both by the method of preparation and by the added materials present in the formulation. In the preparation of compressed tablets, the formulator also must be cognizant of the effect that the ingredients and methods of preparation may have on the availability of the active ingredients and, hence, the therapeutic efficacy of the dosage form. In response to a request by physicians to change a dicumarol tablet so that it might be broken more easily, a Canadian company reformulated to make a large tablet with a score. Subsequent use of the tablet, containing the same amount of drug substance as the previous tablet, resulted in complaints that larger-than-usual doses were needed to produce the same therapeutic response. On the other hand, literature reports indicate that the reformulation of a commercial digoxin tablet resulted in a tablet that, although containing the same quantity of drug substance, gave the desired clinical response at half its original dose. Methods and principles that can be used to assess the effects of excipients and additives on drug absorption have been reviewed.[2,14,15] See Chapters 38, 53, and 58.

TABLET INGREDIENTS

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials. The latter are known as additives or *excipients*. They may be classified according to the part they play in the finished tablet. The first group contains those that help to impart satisfactory processing and compression characteristics to the formulation. These include diluents, binders, glidants, and lubricants. The second group of added substances helps to give additional desirable physical characteristics to the finished tablet. Included in this group are disintegrants, colors, and, in the case of chewable tablets, flavors and sweetening agents, and in the case of controlled-release tablets, polymers or waxes or other solubility-retarding materials.

Although the term *inert* has been applied to these added materials, it is becoming increasingly apparent that there is an important relationship between the properties of the excipients and the dosage forms containing them. Preformulation studies demonstrate their influence on stability, bioavailability, and the processes by which the dosage forms are prepared. The need for acquiring more information and use standards for excipients has been recognized in a joint venture of the Academy of Pharmaceutical Sciences and the Council of the Pharmaceutical Society of Great Britain. The result is called the *Handbook of Pharmaceutical Excipients*. This reference now is distributed widely throughout the world.[16]

Diluents

Frequently, the single dose of the active ingredient is small, and an inert substance is added to increase the bulk to make the tablet a practical size for compression. Compressed tablets of dexamethasone contain 0.75 mg steroid per tablet; hence, it is obvious that another material must be added to make tableting possible. Diluents used for this purpose include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such tablets commonly are called *chewable tablets*. Upon chewing, properly prepared tablets will disintegrate smoothly at a satisfactory rate, have a pleasant taste and feel, and leave no unpleasant aftertaste in the mouth. Diluents used as excipients for direct compression formulas have been subjected to prior processing to give them flowability and compressibility. These are discussed under *Direct Compression*, page 869.

Most formulators of immediate-release tablets tend to use consistently only one or two diluents selected from the above group in their tablet formulations. Usually, these have been selected on the basis of experience and cost factors. However, in the formulation of new therapeutic agents, the compatibility of the diluents with the drug must be considered; eg, calcium salts used as diluents for the broad-spectrum antibiotic tetracycline have been shown to interfere with the drug's absorption from the GI tract. When drug substances have low water solubility, it is recommended that water-soluble diluents be used to avoid possible bioavailability problems. Highly adsorbent substances, eg, bentonite and kaolin, are to be avoided in making tablets of drugs used clinically in small dosage, such as the cardiac glycosides, alkaloids, and the synthetic estrogens. These drug substances may be adsorbed after administration. The combination of amine bases with lactose, or amine salts with lactose in the presence of an alkaline lubricant results in tablets that discolor on aging.

Microcrystalline cellulose (Avicel) usually is used as an excipient in direct-compression formulas. However, its presence in 5 to 15% concentrations in wet granulations has been shown to be beneficial in the granulation and drying processes in minimizing case-hardening of the tablets and in reducing tablet mottling.

Many ingredients are used for several different purposes, even within the same formulation; eg, corn starch can be used in paste form as a binder. When added in drug or suspension form, it is a good disintegrant. Even though these two uses are to achieve opposite goals, some tablet formulas use corn starch in both ways. In some controlled-release formulas, the polymer hydroxypropylmethylcellulose (HPMC) is used both as an aid to prolong the release from the tablet as well as a film-former in the tablet coating. Therefore, most excipients used in formulating tablets and capsules have many uses, and a thorough understanding of their properties and limitations is necessary to use them rationally.

Binders

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators. They impart a cohesiveness to the tablet formulation that ensures the tablet remaining intact after compression, as well as improving the free-flowing qualities by the formulation of granules of desired hardness and size. Materials commonly used as binders include starch, gelatin, and sugars such as sucrose, glucose, dextrose, molasses, and lactose. Natural and synthetic gums that have been used include acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, Veegum, and larch arabogalactan. Other agents that may be considered binders under certain circumstances are polyethylene glycol, ethylcellulose, waxes, water, and alcohol.

The quantity of binder used has considerable influence on the characteristics of the compressed tablets. The use of too much binder or too strong a binder will make a hard tablet that will not disintegrate easily and will cause excessive wear of punches and dies. Differences in binders used for CT Tolbutamide resulted in differences in hypoglycemic effects observed clinically. Materials that have no cohesive qualities of their own will require a stronger binder than those with these qualities. Alcohol and water are not binders in the true sense of the word, but because of their solvent action on some ingredients such as lactose, starch, and celluloses, they change the powdered material to granules, and the residual moisture retained enables the materials to adhere together when compressed.

Binders are used both as a solution and in a dry form, depending on the other ingredients in the formulation and the method of preparation. However, several *pregelatinized* starches available are intended to be added in the dry form so

that water alone can be used as the granulating solution. The same amount of binder in solution will be more effective than if it were dispersed in a dry form and moistened with the solvent. By the latter procedure, the binding agent is not as effective in reaching and wetting each of the particles within the mass of powders. Each of the particles in a powder blend has a coating of adsorbed air on its surface, and it is this film that must be penetrated before the powders can be wetted by the binder solution. After wetting, a certain period of time is necessary to dissolve the binder completely and make it completely available for use. Since powders differ with respect to the ease with which they can be wetted and their rate of solubilization, it is preferable to incorporate the binding agent in solution. By this technique it often is possible to gain effective binding with a lower concentration of binder.

The direct-compression method for preparing tablets (see page 869) requires a material that is not only free-flowing but also sufficiently cohesive to act as a binder. This use has been described for a number of materials including microcrystalline cellulose, microcrystalline dextrose, amylose, and polyvinylpyrrolidone. It has been postulated that microcrystalline cellulose is a special form of cellulose fibril in which the individual crystallites are held together largely by hydrogen bonding. The disintegration of tablets containing the cellulose occurs by breaking the intercrystallite bonds by the disintegrating medium.

STARCH PASTE—Corn starch is used widely as a binder. The concentration may vary from 10 to 20%. It usually is prepared as it is to be used, by dispersing corn starch in sufficient cold purified water to make a 5 to 10% *w/w* suspension and warming in a water bath with continuous stirring until a translucent paste forms. It has been observed that during paste formation, not all of the starch is hydrolyzed. Starch paste then is not only useful as a binder, but also as a method to incorporate some disintegrant inside the granules.

GELATIN SOLUTION—Gelatin generally is used as a 10 to 20% solution; gelatin solutions should be prepared freshly as needed and used while warm or they will solidify. The gelatin is added to cold purified water and allowed to stand until it is hydrated. It then is warmed in a water bath to dissolve the gelatin, and the solution is made up to the final volume on a weight basis to give the concentration desired.

CELLULOSIC SOLUTIONS—Various cellulosics have been used as binders in solution form. Hydroxypropylmethylcellulose (HPMC) has been used widely in this regard. Typical of a number of cellulosics, HPMC is more soluble in cold water than hot. It also is more dispersable in hot water than cold. Hence, to obtain a good, smooth gel that is free from lumps or *fisheyes*, it is necessary to add the HPMC in hot, almost boiling water and, under agitation, cool the mixture down as quickly as possible, as low as possible. Other water-soluble cellulosics such as hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC) have been used successfully in solution as binders.

Not all cellulosics are soluble in water. Ethylcellulose can be used effectively when dissolved in alcohol or as a dry binder that then is wetted with alcohol. It is used as a binder for materials that are moisture-sensitive.

POLYVINYLPYRROLIDONE—PVP can be used as an aqueous or alcoholic solution, and this versatility has increased its popularity. Concentrations range from 2% and vary considerably.

It will be noted that binder solutions usually are made up to weight rather than volume. This is to enable the formulator to determine the weight of the solids that have been added to the tablet granulation in the binding solution. This becomes part of the total weight of the granulation and must be taken into consideration in determining the weight of the compressed tablet, which will contain the stated amount of the therapeutic agent.

As can be seen by the list of binders in this chapter, most modern binders used in solution are polymeric. Because of this, the flow or spreadability of these solutions becomes important when selecting the appropriate granulating equipment. The rheology of polymeric solutions is a fascinating subject in and of itself and should be considered for these materials.

Lubricants

Lubricants have a number of functions in tablet manufacture. They prevent adhesion of the tablet material to the surface of the dies and punches, reduce interparticle friction, facilitate the ejection of the tablets from the die cavity, and may improve the rate of flow of the tablet granulation. Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils, and polyethylene glycol (PEG). Most lubricants, with the exception of talc, are used in concentrations below 1%. When used alone, talc may require concentrations as high as 5%. Lubricants are in most cases hydrophobic materials. Poor selection or excessive amounts can result in *waterproofing* the tablets, resulting in poor tablet disintegration and/or delayed dissolution of the drug substance.

The addition of the proper lubricant is highly desirable if the material to be tableted tends to stick to the punches and dies. Immediately after compression, most tablets have the tendency to expand and will bind and stick to the side of the die. The choice of the proper lubricant will overcome this effectively.

The method of adding a lubricant to a granulation is important if the material is to perform its function satisfactorily. The lubricant should be divided finely by passing it through a 60- to 100-mesh nylon cloth onto the granulation. In production this is called *bolting* the lubricant. After adding the lubricant, the granulation is tumbled or mixed gently to distribute the lubricant without coating the particles too well or breaking them down to finer particles. Some research has concluded that the order of mixing of lubricants and other excipients can have a profound effect on the performance of the final dosage form. Thus, attention to the mixing process itself is just as important as the selection of lubricant materials.

These process variables can be seen in the prolonged blending of a lubricant in a granulation. Overblending materially can affect the hardness, disintegration time, and dissolution performance of the resultant tablets.

The quantity of lubricant varies, being as low as 0.1% and, in some cases, as high as 5%. Lubricants have been added to the granulating agents in the form of suspensions or emulsions. This technique serves to reduce the number of operational procedures and thus reduce the processing time.

In selecting a lubricant, proper attention must be given to its compatibility with the drug agent. Perhaps the most widely investigated drug is acetylsalicylic acid. Different talcs varied significantly the stability of aspirin. Talc with a high calcium content and a high loss on ignition was associated with increased aspirin decomposition. From a stability standpoint, the relative acceptability of tablet lubricants for combination with aspirin was found to decrease in the following order: hydrogenated vegetable oil, stearic acid, talc, and aluminum stearate.

The primary problem in the preparation of a water-soluble tablet is the selection of a satisfactory lubricant. Soluble lubricants reported to be effective include sodium benzoate, a mixture of sodium benzoate and sodium acetate, sodium chloride, leucine, and Carbowax 4000. However, it has been suggested that formulations used to prepare water-soluble tablets may represent a number of compromises between compression efficiency and water solubility. While magnesium stearate is one of the most widely used lubricants, its hydrophobic properties can retard disintegration and dissolution. To overcome these waterproofing characteristics, sodium lauryl sulfate sometimes is included. One compound found to have the lubricating properties of magnesium stearate without its disadvantages is magnesium lauryl sulfate. Its safety for use in pharmaceuticals has not been established.